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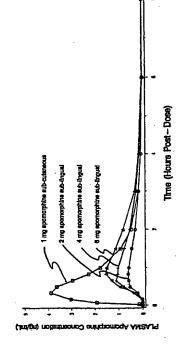
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(57) Abstract

The present invention provides, in one embodiment, a method of normalizing the timing of sexual respons to a mammal comprising the administration of an amount of a central nervous system exacual respons inflation in an amount entiriest no produce gentlat vascibilation but less than the amount required to produce effective vascongestive arousal. The method is applicable not only to adjusting or normalizing the timing of sexual response in humans, but in the bree-ding of valuable commercial animals such as horses, cattle, sheep, swine and the like and domesticated pets such as dogs and cats. In an alternative embodiment, the present invention provides a method for the prophylactic reatment of hospit-erm tissue degrathion in the gential organs comprising the administration to a mannam of ne central hervous system essual response initiator in an amount sufficient to produce genilal vascillation but less than the amount required to produce effective vasocongestive arousal. The preferred central nervous system sexual response initiator is apomorphime or a pharmaceutically acceptable acid addition salt thereof.

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METHODS FOR THE NORMALIZATION OF SEXUAL RESPONSE AND AMELIORATION OF LONG TERM GENITAL TISSUE DEGRADATION

Technical Field

The present application relates to pharmaceutical formulations and to medical methods of treatment. More particularly, the present invention concerns the use of a compound which acts as a central nervous system sexual response initiator for the normalization of the timing of sexual response in humans and for the prophylaxis or treatment of long-term damage to genital organ.

Background of the Invention

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responses deemed to fall within the norm, there is a frequent orgasm. The timing of these steps between partners engaging Proper sexual functioning in men and women depends upon appropriate anticipatory mental set ("desire"), 2) effective psychological, or sometimes biogenic, dysfunction in one or vasocongestive arousal (an erection in the male sufficient engaging in sex is important and often mis-matched due to both of the partners. Even in sex partners having sexual in sexual relations is mediated by one or more of several mesencephalon or mid-brain. These pathways include those termed the serotonergic, dopaminergic, oxytocinergic, and aspects or parameters of sexual response between partners nitroxidergic mid-brain pathways. Timing of the various a combination of steps including 1) establishment of the erection, vaginal engorgement and lubrication), and 3) for vaginal penetration and, in the female, clitoral compounds which act in neurological pathways in the mis-match of the timing of response.

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Orgasm in the male includes the sensation of emission followed by ejaculation. The sensation of emission is one of ejaculatory inevitability and is mediated by contractions of the prostate, seminal vesicles, and urethra. Orgasm in the female is accompanied by contractions of the muscles that line the wall of the outer third of the vagina. In both sexes, generalized muscular tension, perineal contractions and involuntary pelvic thrusting usually occur. Orgasm is followed by resolution, a sense of general relaxation, wellbeing, and muscular relaxation. During this phase men are

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physiologically refractory to further erection and orgasm for a variable period of time. In contrast, women may be able to respond to additional stimulation almost immediately.

Sexual response is mediated by a balanced interplay between the sympathetic and parasympathetic nervous systems. Vasocongestion, or erectile tumescence, is largely mediated by parasympathetic (cholinergic) outflow, whereas orgasm is predominantly sympathetic (adrenergic). Ejaculation is almost entirely sympathetic, whereas emission involves a much more finely balanced combination of sympathetic and parasympathetic stimulation.

Normal biological response in humans results in ejaculation typically within about two minutes or more following vaginal penetration. Most women are unable to reach orgasm within this short period of time, one cause of the problem of inappropriate timing of sexual response between sexual partners, even when the sexual responses of both are within physiological norms. In the case of the sexual dysfunction in males known as premature ejaculation, the problem is further exacerbated.

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premature ejaculation in males may have either a psychogenic or biogenic origin in a particular individual, and various treatment methods have been suggested. These include counseling and techniques for learning control of ejaculation and the use of serotonin re-uptake inhibitors such as fluoxetine hydrochloride (Prozac®) and sertraline hydrochloride (Zoloft®) to delay the onset of the sensation of emission.

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The problem of inappropriate timing of sexual response is not limited to the human species, but occurs also in lower mammals as well, for example, in the breeding of valuable commercial animals such as horses, cattle, sheep, swine and the like and domesticated pets such as dogs and cats.

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United States Patent (Ser. No. 08/546,498) discloses a method of ameliorating erectile dysfunction in a male patient by administration of apomorphine or a salt thereof in an amount sufficient to induce an erection adequate for vaginal penetration, but less than that which induces nausea.

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The need remains, however, for the development of effective means to normalize the timing of sexual response in mammals, including humans and, in particular, in those cases involving premature ejaculation in human males.

In addition, there is a need for agents for the prophylaxis and treatment of long-term degradative effects or damage to genital organ tissues in mammals.

BRIEF DESCRIPTION OF THE DRAWING FIGURE

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FIGURE 1 is a linear plot of the mean plasma concentrations of apomorphine following the administration of sub-cutaneous and sublingual doses of apomorphine.

SUMMARY OF THE INVENTION

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It has been found, in accordance with one embodiment of the present invention that the acute administration of an agent which acts upon mid-brain dopaminergic, serotonergic, oxytocinergic or nitroxidergic pathways to initiate mammalian sexual response in an amount which is insufficient to produce effective vasocongestive arousal, but is sufficient to produce increased genital vasodilation, acts to normalize the timing of sexual response between sexual partners.

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In another embodiment, the present invention provides a method of ameliorating long-term genital organ tissue damage comprising the chronic administration of a mammalian central nervous system sexual response initiator in an amount less than that required to produce a vasocongestive arousal in said mammal, but sufficient to cause vasodilation in the genitalia.

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DETAILED DESCRIPTION

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In the first embodiment of the invention, a central nervous system sexual response initiator is administered to a mammal in an acute dose to one or both partners in the period just prior to sexual intercourse, preferably in a dose insufficient to cause effective vasocongestive arousal, but sufficient to increase genital vasodilation to aid in the

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normalization of the timing of sexual response between the sexual partners. The drug is administered during the period between about two to about one-hundred-twenty minutes prior to sexual relations, preferably in the period between about two and sixty minutes prior to sexual relations.

In the case where the male suffers from the sexual dysfunction termed sexual arousal disorder (lnability to attain the psychic readiness, and/or sustain an erection satisfactory for normal coitus) or the condition known as premature ejaculation, the drug is administered to the male partner. Where the female suffers sexual arousal disorder (persistent or recurrent failure to attain the psychic readiness and/or maintain the lubrication-swelling response), the drug is administered to the female partner. In the case of both the male and female partners, the drug may also be co-administered with a low dose of androgen to potentiate the effect of the mid-brain pathway mediator drug.

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By "androgen" is meant testosterone, dihydrotestosterone, and dehydroepiandrostenedione, either in their free base forms or in the form of a salt or pro-drug.

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The terms "acute dose" or "acute administration" of the drug mean the scheduled administration of the drug to the patient on an as-needed basis.

The term "central nervous system sexual response initiator" denotes a compound which acts in any of the dopaminergic, serotonergic, oxytocinergic or nitroxidergic mammalian mid-brain pathways to initiate a sexual response.

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Dopaminergic pathway initiators include apomorphine, bromocriptine, lisuride, methergoline, pergolide, piribidil, and quinpirole.

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Serotonergic pathway initiators include serotonin receptor agonists such as 1-(2,5-dimethoxy-4-lodophenyl)-1-aminopropane, 5-methoxytryptamine, α-methyl-5-hydroxytryptamine, 2-methyl-5-hydroxytryptamine, N-acetyl-5-hydroxytryptamine buspirone, and sumatriptin.

Oxytocinergic pathway initiators include oxytocin analogues such as isotocin, carbetocin, Lys-conopressin,

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deaminooxytocin, mesotocin, antocin, glumitocin, aspargitocin, valitocin, asvatocin, phasvatocin, and seritocin.

The preferred central nervous system sexual response initiator for use in the methods of the present invention is apomorphine or one of its salts or pro-drug forms.

Apomorphine, (R)-5,6,6a,7-tetrahydro-6-methyl-(4H)-dibenzo[de,g]quinoline-10,11-diol, is a derivative of morphine obtained by treatment of the latter with concentrated hydrochloric acid (L. Small, et al., <u>J. Org.</u> <u>Chem.</u>, 5: 334 (1940)) or by heating morphine with zinc chloride (Mayer, <u>Ber.</u>, 4: 171 (1871)). The compound has the chemical structure:

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Apomorphine

and possesses a chiral center at position 6a. The total synthesis of the racemic mixture is reported by J. L. Neumeyer, et al., <u>J. Pharm. Sci.</u>, 59:1850 (1970) and the synthesis of the separate enanthomers by V. J. Ram and J. L. Neumeyer, <u>J. Org. Chem.</u>, 46: 2830 (1981).

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The compound possesses a basic nitrogen atom at position 6 and is thus capable of existing in the free base form as well as acid addition salt forms. The compound may be administered as the free base or in the form of one of its pharmaceutically acceptable salts or pro-drug derivatives.

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As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity,

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acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts are prepared in situ during the final isolation and purification of the compounds of the invention, picrate, pivalate, propionate, stearate, succinate, sulfate, amino group formed with inorganic acids such as hydrochloric succinic acid or malonic acid or by using other methods used maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, Pharmaceutically acceptable salts are well known in the art. acid, hydrobromic acid, phosphoric acid, sulfuric acid and for example, S. M. Berge, et al. describe pharmaceutically perchloric acid or with organic acids such as acetic acid, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, in the art such as ion exchange. Other pharmaceutically acceptable, nontoxic acid addition salts are salts of an or separately by reacting the free base function with a tartrate, thiocyanate, p-toluenesulfonate, undecanoate, lactobionate, lactate, laurate, lauryl sulfate, malate, acceptable salts include adipate, alginate, ascorbate, pectinate, persulfate, 3-phenylpropionate, phosphate, oxalic acid, maleic acid, tartaric acid, citric acid, glycerophosphate, gluconate, hemisulfate, heptanoate, suitable organic acid. Examples of pharmaceutically cyclopentanepropionate, digluconate, dodecylsulfate, Irritation, allergic response and the like, and are ethanesulfonate, formate, fumarate, glucoheptonate, hexanoate, hydrotodide, 2-hydroxy-ethanesulfonate, commensurate with a reasonable benefit/risk ratio. butyrate, camphorate, camphorsulfonate, citrate, valerate salts, and the like.

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The term "pro-drug" refers to compounds that are rapidly transformed in vivo to yield the parent compound, as for example, by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the pro-drug concept in "Pro-drugs as Novel Delivery Systems", Vol. 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Examples of esters useful as pro-drugs for compounds containing carboxyl groups may be found on pages 14-21 of "Bioreversible

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Carriers in Drug Design: Theory and Application," edited by E.B. Roche, Pergamon Press (1987). The term "pro-drug ester group" refers to any of several nethoxymethyl, as well as other such groups known in the art. ester-forming groups that are hydrolyzed under physiological pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and conditions. Examples of pro-drug ester groups include

each alkyl or alkenyl moiety advantageously has not more than acceptable aliphatic carboxylic acids, particularly alkanoic, those that break down readily in the human body to leave the ester" refers to esters which hydrolyze in vivo and include As used herein, the term "pharmaceutically acceptable include, for example, those derived from pharmaceutically parent compound or a salt thereof. Sultable ester groups formates, acetates, propionates, butryates, acrylates and alkenoic, cycloalkanoic and alkanedioic acids, in which carbon atoms. Examples of particular esters includes ethylsuccinates.

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duration of erection in the male and, in the female, increase time of onset, duration, and likelihood of a sexual response so that these parameters tend toward the normal response for timing of sexual response in a human is meant adjusting the sexual response can include delay of onset of the sensation of emission, delay of ejaculation, and prolongation of the a human under the given circumstances. Normalization of By the term "normalizing" or "normalization" of the in the likelihood of clitoral erection, swelling and lubrication.

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recurrent ejaculation before, upon, or shortly after vaginal The term "premature ejaculation" in the male is meant penetration. More generally, the term can be defined as the sexual dysfunction characterized by persistent or ejaculation occurring before the individual wishes.

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engorgement and swelling of the vagina and labia. The term The term "vasocongestive arousal" means, in the male, tumescent penile erection, but insufficient for vaginal penetration and, in the female, clitoral erection and

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effective vasocongestive arousal" means, in the male, an

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erection sufficient for vaginal penetration.

a representative drug of the class of compounds contemplated The following study illustrates the use of apomorphine, sexual response by administration of the drug to males to by the present invention, for normalizing the timing of extend the duration of erection.

placebo in one of the treatment periods, and a dose (2 mg, 4 This arrangement resulted in approximately one-third of the controlled, three-armed study was conducted on 370 patients mg, or 6 mg) of apomorphine in the other treatment period. organic component. For each sequence, patients received A multi-center, double-blind, randomized, placebodiagnosed with male erectile dysfunction with no major patients receiving one of the three apomorphine doses.

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with the use of the study drug and antiemetic and concomitant their sexual partners were instructed to attempt intercourse recorded in the patient diary. The data from these studies questionnaire recorded the date and time the study drug was taken, an evaluation of the erection, whether or not sexual intercourse had occurred, and satisfaction associated with taken, a questionnaire was completed by the patient and by recorded the latency and duration of erections associated medication usage and any adverse effects. If an erection occurred after administration to the patient of the study drug, the duration of erection and time-to-erection were a minimum of twice weekly. Each time the study drug was During treatment periods of the study, patients and each attempt. The patient also completed a diary which the partner and mailed to the study sponsor. The are presented in Tables 1-4.

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apomorphine versus placebo in each case for all attempts. If Table 1 shows the mean durations in minutes of erections differences in the mean durations of erections between drug the attempt failed to produce an erection, a value of zero minutes was used in the statistical analysis. The data in Table 1 indicate dose-dependent, statistically significant for patients receiving a dose (2 mg, 4 mg, or 6 mg) of

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and placebo, with the mean values being lowered by overall by -6-

inclusion of zero value data from attempts which did not

Table 2 shows the data for only those attempts which did result in an erection. The data in Table 2 also indicate a duration of erection, with a difference of almost 5 minutes between patients taking the 6 mg dose and those receiving dose-dependent, statistically significant difference of result in an erection. placebo

placebo, but the differences probably reflect the inclusion in Table 3 presents the median time to erection for patients minutes time-to-erection was used in the statistical analysis. between patients receiving apomorphine and those receiving involved in the study and shows data for all attempts. In those cases where no erection was achieved, a value of 60 the data of 60 minute values for those cases in which no the data in Table 3 show differences in latency periods erection was achieved.

Table 4 shows the data only for patients where an attempt show that there was no statistically significant difference in was successful in achieving an erection. The data in Table 4 the median time-to-erection between patients receiving the drug and those receiving placebo, with a median time-toerection of about 12 minutes.

compared to placebo, but resulted in a significant increase in longer time typically required for females to reach orgasm in Tables 1-4 is that administration of apomorphine at the doses the cycle of sexual response, administration of the drug to One conclusion to be drawn from the data presented in erection despite effects on the duration of erection when the male partner serves to normalize the timing of sexual the duration of erection. Keeping in mind the generally tested did not shorten or prolong the time of onset of response between coital partners.

The median time-to-erection in patients receiving the study drug at all doses tested was approximately 12 minutes. The data in Tables 3 and 4 are instructive in another However, a pharmacokinetic evaluation of apomorphine,

An "attempt" is defined to be the taking of the

and patient within sequence. scandard errors and P-values

efficacy question on the patient questionnaire.

t Statistically significant at 2 = 0.001.

5-√ 2 1ue	branasta To rorra The Mean	ni eonerellid anseM (Minutes)	Mean (Minutes)	To redmuM editest	JaemiserT	Study Arm
			£6£.8	TTT	Drnd	Apomorphine 6 mg
<0,001 ²	£88.0	861.2	3.255	TTT	Placebo]
			£06.8	129	DEAG	Apomorphine 4 mg
τ100,0>	759.0	873.5	3.325	129	Placebo]
			020.2	I32	Dzug	Apomorphine 2 mg
τ100.0>	₽£2.0	9E6.1	₽80,5	732	Placebo	j

an erection, an duration of zero minutes was used in the statistical

study drug and completion by the patient of the appropriate

Analysis was done on average duration of erection for each patient during each period.

Based on All Attempts Duration of Erection A lo eletysis of A Results of Stat ysis of Average Durations

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Duration of Erection Feaults of Statistions Results of Statistical Analysis of Average Durations Based on All Attempts Where Erection Was Achieved

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Treatment Difference Standard Torra	Difference in Mean (Minutes)	Mean (Minutes)	Number of Patients	JamiserT nemipeR	study Arm
		96.51	07	Drnd	Pomorphine 6 mg
626.0	4.925	0.030	0.6	Placebo	
		12.49	98	Drad	Purphine 4 mg
698.0	3.458	820.6	98	Placebo	
		10.82	83	DERT	Apomorphine 2 mg
876.0	ITBTI	ZT0°6	€8	Placebo	

Notes : An "attempt" is defined to be the taking of the study drug and completion by the patient of the appropriate efficacy question on the patient questionnaire.

not result in an erection were not used in the statistical analysis. Analysis was done on average duration of erection for each patient during each period. Attempts which did

All means and standard errors are from an ANOVA model with effects for treatment, period, sequence, and patient within sequence.

Time to Erection Kaplan-Meier Estimation of Median Time to Erection Kaplan-Meier Estimation of Median Time to Erection E eldsT

95% Confidence Interval	nsibeM (BejuniM)	Mumber of states	TreatserT Regimen	mia ybuje
26,50 36,67	55.15	III	Drag	Apomorphine 6 mg
8.52 - 57.5₽	02.74	III	Placebo	for a great depending
72.50 - 42.2E	36.00	TET	Drag	Apomorphine 4 mg
E8.02 - E7.24	87.7 <u>p</u>	TET	. Буясеро	5
25.89 - £5.25	71.Sp	SET	Drag	pm S eninqromoqA
86.42 - 38.44	00.02	732	Placebo	6

Notes : An "attempt" is defined to be the taking of the study drug and completion by the patient of the appropriate efficacy question on the patient questionnaire.

Analysis was done on average time until erection, a time until erection of 60 minutes was used. For attempts which did not result in an erection, a time until erection of 60 minutes was used.

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Time to Erection Kaplan-Meier Estimation of Median Time to Ered Based on Attempts When Erection Occurred to Erection A eldeT

95% Confidence Interval	TreatfearT EnseM	Number of states	dnemdseaT RemipeR	Study Arm
79.81 00.01	28.21	96	DENG	Apomorphine 6 mg
10.00 14.00	73.11	82	Placebo	S
00.01 00.01	12.61	011		Apomorphine 4 mg
10.00 15.00	27.51	Þ6	Placebo	
00.21 00.01	£E.11	109		Apomorphine 2 mg
10°30 12°00	12.42	26	Placebo	

Analysis was done on average time until erection for each patient during each period. Notes : An "attempt" is defined to be the taking of the study drug and completion by the patient of the appropriate efficacy question on the patient questionnaire.

is based on the first eight attempts.

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observed in patients who had experienced difficulty achieving administration. As shown by examination of Figure 1, at that therapeutic effect beginning at 12 minutes following buccal generally ranging between about 0.02 ng/mL and 0.25 ng/mL median time-to-erection is about 12 minutes, one-fifth the apomorphine and about 20 minutes following administration, effect. Production of plasma apomorphine concentrations The data presented in Tables 3 and 4 show that the about 0.25 ng/mL are sufficient to cause a therapeutic following buccal administration. Since erections were time required to reach maximum plasma concentrations ø

the plasma concentration curves for all three doses tested (2 of the data indicate that plasma apomorphine levels less than producing the desired effect at lower doses than initially preferred for the method of this embodiment of the invention. to one-fourth maximum blood serum levels, indicating that it an erection in the absence of the drug, the data thus show a believed necessary. In the period between administration of mg, 4 mg, and 6 mg) show similar profiles and interpolation point in time, the drug has reached approximately one-fifth

the dose administered to the patient in this

Preferably,

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embodiment of the invention is generally sufficient to

produce mean plasma levels less than about 0.25 ng/mL,

preferably in the range of about 0.02 ng/mL to about 0.25

duration of erection and aids in normalizing

extending the the timing of intercourse

sexual responses between the partners

sufficient to increase genital blood flow is effective in

than that required for effective congestive arousal,

Thus the administration of a dose of apomorphine lower

illustrated in the graph depicted in Figure 1, shows that the minutes. However, as shown by the pharmacokinetic curves in time required to reach maximum blood serum levels following lingual administration (the formulation used in the studies the maximum plasma concentrations following subsubcutaneous delívery of apomorphine is approximately 15 presented in Tables 1-4), was not reached until about 60 minutes following administration. Figure 1,

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embodiment of the invention, the mode of delivery of the drug on an as-needed basis in the time period immediately prior to Cormulation which rapidly delivers the drug to the system and sexual intercourse. The drug is preferably administered in a for example, the drug may be rapidly delivered to the system by means of a liquid formulation applied sub-lingually; by a buccally; by means of a suppository formulation administered intravaginally or rectally; by a powder, gel, or suspension, tablet, lozenge, or lollipop held in the mouth and absorbed is by acute administration; that is, in a dose administered formulation arts which accomplishes this means may be used. any method known to the practitioner of the pharmaceutical These serum levels translate into doses generally In this ranging between about 0.02 mg to about 4 mg per dose, depending upon the formulation delivery system. or an intra-nasal spray formulation.

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The drug may also be administered in a sterile parenteral formulation by sub-cutaneous or intramuscular route, although sub-lingual, buccal, intra-nasal, and suppository formulations are preferred because of their greater ease of administration and the resulting greater potential for patient acceptance.

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Depending upon the T_{max} for a particular formulation, the drug is administered in the time period immediately prior to sexual intercourse, generally during the period between about 2 minutes and 120 minutes prior to sexual relations, preferably during the period between about 2 minutes and about 60 minutes prior to sexual relations.

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In cases where the male sex partner suffers from sexual arousal disorder, or premature ejaculation, the drug is administered to the male, optionally with the coadministration of a low dose of androgen. In those instances where the female sex partner suffers from sexual arousal disorder, the drug is administered to the female, optionally with co-administration of a low dose of androgen.

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By "co-administration" is meant 1) the administration of an androgen in a separate dosage form prior to administration of apomorphine, taking into account the particular

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pharmacokinetic profile of the androgen, and 2) the concomitant administration of the androgen and apomorphine in those cases where the pharmacokinetic profiles of the two drugs are similar. In concomitant administration of apomorphine and an androgen, the two drugs may be administered in a single dosage form, or may be administered at the same time in separate dosage forms.

In studies with female rats, response to apomorphine was observed when treated with low doses of testosterone. Animals treated with a combination of apomorphine and testosterone exhibited lordosis, genital grooming and other behaviors typically associated with sexual arousal. Suitable androgens for use in this embodiment of the invention include testosterone, dihydrotestosterone, and dehydrocepiandrostenedione with testosterone being particularly preferred. When co-administration of an androgen is utilized in this method of the invention, the androgen is given is doses sufficient to produce plasma concentrations of about 1 nmol/L to 200 nmol/L.

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As would be apparent to a person of ordinary skill in the art, it is reasonable to use the rat as a model for the affected vascular systems discussed herein such as, for example, the pudendal and penile vasculature, and to extend such studies to appropriate dosages and therapies for other subjects such as higher mammals and humans. As evidenced by Mordenti, "Man versus Beast: Pharmacokinetic Scaling in Mammals," J. Pharm. Sci., 75: 1028-1040 (1986) and similar articles, dosage forms for animals such as, for example, rats can be and are widely used directly to establish dosage levels in therapeutic applications in higher mammals, including humans

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One of the present inventors contributed to the development of a bioassay of erectile function in a rat model at leastas early as 1991 (J.P.W. Heaton, et al., <u>J. Urol.</u>, 145: 1099-1102 (1991)), and also helped to demonstrate in comparative tests of erectile function in humans and rats, that the narrow effective dose window for an orally administered drug, apomorphine, is almost identical when

suitably adjusted for the differences in body weight as taught by Mordenti, cited above (J.P.W. Heaton, et al., Urology, 45: 200-206 (1995)). an alternative embodiment of the present invention, a this embodiment, the drug is administered on a repetitive or such as a transdermal patch or biodegradeable intramuscular prevent, ameliorate, or reverse the damaging effects to the genital organs of extended periods of vasoconstriction. In example once daily, once weekly, or by a depot formulation recurring scheduled basis over a long period of time, for administered chronically in a low maintenance dose to central nervous system sexual response initiator is depot formulation.

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dose" of a drug refer to the scheduled repetitive and regular idministration of a drug to the patient over a long term. The terms "chronic administration," or "maintenance

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vasodilation of the penis and clitoris increase oxygen levels production and vascular wall remodeling which result in long menlarged clitoris and labia are constricted. As a result, example, a man has three to five erections per night in the typical oxygen concentrations in such tissues are closer to itself, shut down adverse metabolic processes such as TGF-β tissue in the penis and clitoris, as well as vasodilation in these tissues. The higher oxygen levels supplied to term tissue damage. Thus under normal conditions, for body's self-regulating mechanism for vasodilating and venous rather than arterial oxygen levels. Periodic The arteries in a normal flaccid penis and the oxygenating penile tissues.

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For the purposes of this embodiment, it is not necessary Typically a lower dose, sufficient for inducing vasodilation concentrations of apomorphine of less than about 0.2 ng/mL, produce effective vasocongestive arousal, that is, in the and increased blood flow to the genitalia is sufficient, that the drug be administered in an amount necessary to generally daily doses sufficient to produce mean plasma male an erection sufficient for vaginal penetration.

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preferably in the range of about 0.02 ng/mL to about 0.2

obtain a low, steady-state blood serum level of the drug, the rapidly to the system, and typical formulations known in the rasodilation of the genital organs to combat the deleterious suspensions and the like, such as those described below may Since the object of this embodiment of the invention is to effects of restricted blood flow to the organs over time. drug formulation need not be one which delivers the drug concentration of the drug result in tumescence which is art such as tablets, pills, lozenges, syrups, elixirs, insufficient for intercourse, but produce sufficient The maintenance of these low levels of serum employed.

Pharmaceutical Formulations

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pyrogen-free water; isotonic saline; Ringer's solution; ethyl starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl Pharmaceutical compositions suitable for administration semi-solid or liquid filler, diluent, encapsulating material cellulose and cellulose acetate; powdered tragacanth; malt; oil; glycols; such a propylene glycol; esters such as ethyl suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean alcohol, and phosphate buffer solutions, as well as other magnesium hydroxide and aluminum hydroxide; alginic acid; carriers are sugars such as lactose, glucose and sucrose; oleate and ethyl laurate; agar; buffering agents such as naterials which can serve as pharmaceutically acceptable or formulation auxiliary of any type. Some examples of therapeutically effective amount of the drug formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, gelatin; talc; excipients such as cocoa butter and of the drug of the present invention comprise a

non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing

agents, coating agents, sweetening, flavoring and perfuming

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fatty acids such as oleic acid are used in the preparation of Injectables.

or by incorporating sterilizing agents in the form of sterile example, by filtration through a bacterial-retaining filter, solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to The injectable formulations can be sterilized, for

temperature but liquid at body temperature and therefore melt accomplished by the use of a liquid suspension of crystalline to polymer and the nature of the particular polymer employed, preferably suppositories which can be prepared by mixing the polylactide-polyglycolide. Depending upon the ratio of drug dissolution which, in turn, may depend upon crystal size and or amorphous material with poor water solubility. The rate other biodegradable polymers include poly(orthoesters) and In order to prolong the effect of a drug, it is often crystalline form. Alternatively, delayed absorption of a excipients or carriers such as cocoa butter, polyethylene Injectable depot forms are made by forming microencapsule the rate of drug release can be controlled. Examples of poly(anhydrides) Depot injectable formulations are also compounds of this invention with suitable non-irritating of absorption of the drug then depends upon its rate of glycol or a suppository wax which are solid at ambient in the rectum or vaginal cavity and release the active matrices of the drug in biodegradable polymers such as parenterally administered drug form is accomplished by microemulsions which are compatible with body tissues. Compositions for rectal or vaginal administration are subcutaneous or intramuscular injection. This may be dissolving or suspending the drug in an oil vehicle. desirable to slow the absorption of the drug from prepared by entrapping the drug in liposomes or compound.

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capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at Solid dosage forms for oral administration include

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agents, preservatives and antioxidants can also be present in The pharmaceutical compositions of this invention can be the composition, according to the judgment of the formulator. administered to humans and other animals orally, rectally, parenterally, intravaginally, topically (as by powders,

water, Ringer's solution, U.S.P. and isotonic sodium chloride particular, cottonseed, groundnut, corn, germ, olive, castor, inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers ointments, or drops), bucally, or as an oral or nasal spray. polyethylene glycols and fatty acid esters of sorbitan, and solutions, suspensions, syrups and elixirs. In addition to Injectable preparations, using suitable dispersing or wetting agents and suspending conventionally employed as a solvent or suspending medium. agents. The sterile injectable preparation may also be a acceptable vehicles and solvents that may be employed are such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, the active compounds, the liquid dosage forms may contain ethyl acetate, benzyl alcohol, benzyl benzoate, propylene sterile injectable solution, suspension or emulsion in a suspensions may be formulated according to the known art nontoxic parenterally acceptable diluent or solvent, for including synthetic mono- or diglycerides. In addition, glycol, 1,3-butylene glycol, dimethylformamide, oils (in Liquid dosage forms for oral administration include compositions can also include adjuvants such as wetting and sesame oils), glycerol, tetrahydrofurfuryl alcohol, agents, emulsifying and suspending agents, sweetening, for example, sterile injectable aqueous or oleaginous pharmaceutically acceptable emulsions, microemulsions, example, as a solution in 1,3-butanediol. Among the For this purpose any bland fixed oil can be employed mixtures thereof. Besides inert diluents, the oral solution. In addition, sterile, fixed oils are flavoring, and perfuming agents.

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agents and can also be of a composition that they release the manner. Examples of embedding compositions which can be used excipients as lactose or milk sugar as well as high molecular be prepared with coatings and shells such as enteric coatings The solid dosage etarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such such as glycerol, d) disintegrating agents such as agar-agar, forms of tablets, dragees, capsules, pills, and granules can Solid compositions of a similar type may also be employed as carrier such as sodium citrate or dicalcium phosphate and/or glucose, mannitol, and silicic acid, b) binders such as, for as, for example, cetyl alcohol and glycerol monostearate, h) stearate, solid polyethylene glycols, sodium lauryl sulfate, fillers in soft and hard-filled gelatin capsules using such and mixtures thereof. In the case of capsules, tablets and active ingredient(s) only, or preferentially, in a certain a) fillers or extenders such as starches, lactose, sucrose, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants pills, the dosage form may also comprise buffering agents. calcium carbonate, potato or tapioca starch, alginic acid, least one inert, pharmaceutically acceptable excipient or formulating art. They may optionally contain opacifying part of the intestinal tract, optionally, in a delayed ubricants such as talc, calcium stearate, magnesium certain silicates, and sodium carbonate, e) solution absorbents such as kaolin and bentonite clay, and 1) example, carboxymethylcellulose, alginates, gelatin, and other coatings well known in the pharmaceutical weight polyethylene glycols and the like. include polymeric substances and waxes.

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Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such exciplents as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric

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forms for topical or transdermal administration of a compound solid dosage form's the active compound may be admixed with at delayed manner. Examples of embedding compositions which can of this invention include ointments, pastes, creams, lotions, formulation, ear drops, eye ointments, powders and solutions opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in also comprise buffering agents. They may optionally contain active component is admixed under sterile conditions with a Such dosage forms may also comprise, as is normal practice, least one inert diluent such as sucrose, lactose or starch. well known in the pharmaceutical formulating art. In such nagnesium stearate and microcrystalline cellulose. In the coatings, release controlling coatings and other coatings case of capsules, tablets and pills, the dosage forms may a certain part of the intestinal tract, optionally, in a preservatives or buffers as may be required. Ophthalmic gels, powders, solutions, sprays, inhalants or patches. are also contemplated as being within the scope of this additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a pharmaceutically acceptable carrier and any needed be used include polymeric substances and waxes. invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

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Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the

compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

While there have been described and illustrated preferred embodiments of the present invention, one of ordinary skill in the art to which the invention pertains will recognize that various modifications may be made without departing from the scope of the invention as it is defined by the appended claims.

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WHAT IS CLAIMED IS:

- 1. A method of normalizing the timing of sexual response in a mammal comprising the administration of an amount of a central nervous system sexual response initiator in an amount sufficient to produce genital vasodilation but less than the amount required to produce effective vasocongestive arousal in said human.
- 2. A method in accordance with Claim 1 comprising administering said central nervous system sexual response initiator to said mammal during a period of between about to about one-hundred-twenty minutes immediately prior to coitus.
- 3. A method in accordance with Claim I wherein said central nervous system sexual response initiator is selected from such agents which act upon one or more dopaminergic, serotonergic, oxytocinergic or nitroxidergic mid-brain pathways to initiate a sexual response.
- 4. A method in accordance with Claim 3 wherein said central nervous system initiator is a compound acting upon the dopaminergic mid-brain pathway selected from the group consisting of apomorphine, bromocriptine, lisuride, methergoline, pergolide, piribidil, and quinpirole or a pharmaceutically acceptable salt or pro-drug thereof.
- 5. A method in accordance with Claim 3 wherein said central nervous system initiator is a compound acting upon the serotonergic mid-brain pathway selected from the group consisting of 1-(2,5-dimethoxy-4-iodophenyl)-1-aminopropane, 5-methoxytryptamine, a-methyl-5-hydroxytryptamine, 2-methyl-5-hydroxytryptamine, huspirone, and summatriptin or a pharmaceutically acceptable sait or prodrug thereof.

- 6. A method in accordance with Claim 3 wherein said central nervous system initiator is a compound acting upon the oxytocinergic mid-brain pathway selected from the group consisting of isotocin, carbetocin, Lys-conopressin, deaminooxytocin, mesotocin, antocin, glumitocin, aspargitocin, valitocin, asvatocin, phasvatocin, and seritocin.
- 7. A method of normalizing the timing of sexual response in a mammal comprising the administration of an amount of apomorphine or a pharmaceutically acceptable salt or pro-drug thereof in an amount sufficient to produce genital vasodilation but less than that required to produce effective vasocongestive arousal in said human.
- 8. The method according to Claim 7 wherein said apomorphine or pharmaceutically acceptable salt or pro-drug thereof is administered to said mammal during a period of between about two to about one-hundred-twenty minutes immediately prior to coitus.
- 9. The method according to Claim 7 wherein said apomorphine or pharmaceutically acceptable sait or pro-drug thereof is administered to said mammal during a period of between about two to about sixty minutes immediately prior to coitus.
- 10. The method according to Claim 7 wherein said apomorphine or pharmaceutically acceptable salt or pro-drug thereof is administered to said mammal in an amount sufficient to produce plasma apomorphine concentrations less than about 0.25 ng/mL.
- 11. The method according to Claim 7 wherein said apomorphine or pharmaceutically acceptable salt, ester or pro-drug thereof is administered to said mammal in an amount sufficient to produce plasma apomorphine concentrations of a level ranging between about 0.02 ng/mL to about 0.25 ng/mL.

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- 12. The method according to Claim 7 further comprising co-administration of an androgen.
- 13. The method according to Claim 12 wherein said androgen is selected from the group consisting of testosterone, dihydrotestosterone, and dehydrocepiandrostenedione or a pharmaceutically acceptable salt or prodrug thereof.
- 14. The method according to Claim 13 wherein said androgen is testosterone or a pharmaceutically acceptable salt or pro-drug thereof.
- 15. A method of prolonging vasocongestive arousal in a mammal comprising administering to said mammal an amount of apomorphine or a pharmaceutically acceptable salt or pro-drug thereof in an amount sufficient to produce plasma concentrations less than about 0.25 ng/ml.
- 16. The method according to Claim 15 wherein said apomorphine or pharmaceutically acceptable salt or pro-drug thereof is administered to said human in an amount sufficient to produce plasma apomorphine concentrations of a level ranging between about 0.02 ng/mL to about 0.25 ng/mL.
- 17. The method according to Claim 7 wherein said mammal is a human male.
- 18. The method according to Claim 17 wherein said human male suffers from sexual arousal disorder.
- 19. The method according to Claim 17 wherein said human male suffers from premature ejaculation.

- administered to said human male in an amount sufficient to apomorphine or pharmaceutically acceptable salt thereof is produce plasma apomorphine concentrations less than about The method according to Claim 18 wherein said 0.25 ng/mL.
- thereof is administered to said human in an amount sufficient apomorphine or pharmaceutically acceptable salt or pro-drug 21. The method according to Claim 18 wherein said to produce plasma apomorphine concentrations of a level ranging between about 0.02 ng/mL to about 0.25 ng/mL.
- apomorphine or pharmaceutically acceptable salt thereof is administered to said human male in an amount sufficient to produce plasma apomorphine concentrations less than about 22. The method according to Claim 19 wherein said 0.25 ng/mL.
- thereof is administered to said human in an amount sufficient apomorphine or pharmaceutically acceptable salt or pro-drug 23. The method according to Claim 19 wherein said to produce plasma apomorphine concentrations of a level ranging between about 0.02 ng/mL to about 0.25 ng/mL.
- 24. The method according to Claim 7 wherein said mammal is a human female.
- administered to said human female in an amount sufficient to apomorphine or pharmaceutically acceptable salt thereof is produce plasma apomorphine concentrations less than about 25. The method according to Claim 24 wherein said
- administered to said human female in an amount sufficient to produce plasma apomorphine concentrations of a level ranging apomorphine or pharmaceutically acceptable salt thereof is The method according to Claim 25 wherein said between about 0.02 ng/mL to about 0.25 ng/mL. 26.

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- 27. The method according to Claim 23 wherein said human female suffers from sexual arousal disorder.
- administered to said human female in an amount sufficient to apomorphine or pharmaceutically acceptable salt thereof is produce plasma apomorphine concentrations less than about 28. The method according to Claim 27 wherein said 0.25 ng/mL.
- sufficient to produce plasma apomorphine concentrations of a apomorphine or pharmaceutically acceptable salt or pro-drug level ranging between about 0.02 ng/mL to about 0.25 ng/mL. thereof is administered to said human female in an amount 29. The method according to Claim 28 wherein said
- vasodilation in the genitalia but less than that required to term genital organ tissue damage in a mammal comprising the administration of a mammalian central nervous system sexual produce an effective vasocongestive arousal in said mammal. 30. A method of prophylaxis or amelioration of longresponse initiator in an amount sufficient to cause
- central nervous system initiator is selected from compounds 31. A method in accordance with Claim 30 wherein said serotonergic, oxytocinergic or nitroxidergic mid-hrain which act upon one or more mammaltan dopaminergic, pathways to initiate a sexual response.
- 32. A method in accordance with Claim 31 wherein said the dopaminergic mid-brain pathway selected from the group central nervous system initiator is a compound acting upon methergoline, pergolide, piribidil, and quinpirole or pharmaceutically acceptable salt or pro-drug thereof. consisting of apomorphine, bromocriptine, lisuride,

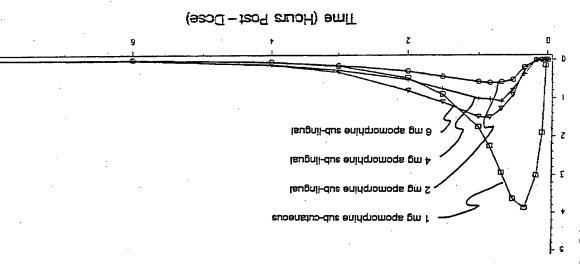
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- 34. A method in accordance with Claim 31 wherein said central nervous system initiator is a compound acting upon the oxytocinergic mid-brain pathway selected from the group consisting of isotocin, carbetocin, lys-conopressin, deaminooxytocin, mesotocin, antocin, glumitocin, aspargitocin, valitocin, asvatocin, phasvatocin, and seritocin.
- 35. A method of ameliorating long-term genital organ tissue damage in a mammal comprising the chronic administration of apomorphine or a pharmaceutically acceptable salt thereof in an amount less than that required to produce effective vasocongestive arousal in said mammal, but sufficient to cause vasodilation in the genitalia.
- 36. The method according to Claim 35 wherein said apomorphine or pharmaceutically acceptable salt thereof is administered to said human in an amount sufficient to produce plasma concentration levels less than about 0.25 ng/ml.
- apomorphine or pharmaceutically acceptable salt thereof is administered to said human in an amount sufficient to produce plasma concentration levels in the range of about 0.02 ng/mL to about 0.25 ng/mL.

Figure 1



PLASMA Apomorphine Concentration (ng/ml.)